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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,003	04/28/2005	Helene Margaret Finney	CELL-0296	1691

20306 7590 06/23/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
06/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,003	FINNEY ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8,9,11,12,17-19,21,25,26,28,30 and 35-37* is/are pending in the application.

4a) Of the above claim(s) *35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,9,11,12,17-19,21,25,26,28,30 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Feb. 12, 2008 has been entered.

Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 35-37 are pending in the instant application. Claims 3-5, 7, 10, 13-16, 20, 22-24, 27, 29, and 31-34 are cancelled. Claims 1, 9, 11, 12, 17, and 19 are amended.

Claims 35 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 are currently under examination.

This application 10/533,003 filed on April 28, 2005 is a 371 of PCT/GB03/04639 filed on 10/28/2003, and claims benefits of foreign application United Kingdom 0225279.9 filed on 10/30/2002.

Sequence compliance

2. The limitation "amino acid residues 166 to 199 of the human inducible co-stimulator" previous recited in claims 1, 9, 11, 12, 17, and 19, has been amended. Claims 1, 9, 11, 12, 17, and 19 now recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL (SEQ

ID NO 1)". A "sequence listing" as set forth in 37 CFR 1.821(a)(1) and (a)(2) has been filed on 02/12/2008 by Applicant and it has been accepted on 02/26/2008.

Claim objection

3. Claims 26 and 30 are objected to because "A host cell" recited in claims 26 and 30 read on a cell in *vivo*, which is a non-elected invention, as Applicant elected Group I directed to *in vitro*, not Group II directed to *in vivo* (See Applicant's response on 11/17/2006 to Restriction Requirement dated 10/19/2006). Amendment of the claims to read "An isolated cell" would limit the claims to the elected invention and would be remedial.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Previous rejection of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claims 1, 9, 11, 12, 17, and 19 have been amended and no longer recites "amino acid residues 166 to 199 of the human inducible co-stimulator". Rather, the amended claims 1, 9, 11, 12, 17, and 19 now recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)".

Claims 2, 6, 8, 9, 11, 12, 17, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Previous rejection of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because the claims have been amended.

Claims 1, 9, 11, 12, 17, and 19 have been amended and no longer recites "amino acid residues 166 to 199 of the human inducible co-stimulator". Rather, the amended claims 1, 9, 11, 12, 17, and 19 now recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)".

Claims 2, 6, 8, 9, 11, 12, 17, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Previous rejection of claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 under 35 U.S.C. 102(b) as being anticipated by Roberts et al., (Roberts et al., PCT/US96/01293, WO 96/23814, listed in IDS filed by the applicants), is ***withdrawn*** because the claims have been amended.

Claims 1, 9, 11, 12, 17, and 19 have been amended to recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)". Roberts et al. does not teach SEQ ID No: 1. Claims 2, 6, 9, 11, 12, 17, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

7. Previous rejection of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 under 35 U.S.C. 102(b) as being anticipated by Finney et al. (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002, listed in IDS filed by the applicants), is ***withdrawn*** because the claims have been amended.

Claims 1, 9, 11, 12, 17, and 19 have been amended to recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)". Finney et al. does not teach SEQ ID No: 1. Claims 2, 6, 8, 9, 11, 12, 17, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

8. Previous rejection of claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 under 35 U.S.C. 102(b) as being anticipated by Maher et al. (Maher et al., Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor. *Nat Biotechnol.* 20(1): 70-5, Jan. 2002; listed in the IDS filed by the applicants) as evidenced by

Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants), is ***withdrawn*** because the claims have been amended.

Claims 1, 9, 11, 12, 17, and 19 have been amended to recite "the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)".

Maher et al. does not teach SEQ ID No: 1. Claims 2, 6, 9, 11, 12, 17, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

The following rejections under 35 U.S.C. 103(a) are necessitated claim amendments filed on 02/26/2008.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Maher et al.** (Maher et al., Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor. *Nat Biotechnol.* 20(1): 70-5, Jan. 2002; listed in the IDS filed by the applicants) in view of **Hutloff et al.** (Hutloff et al.,

ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants).

Claim interpretation: It is noted that "A host cell" recited in claims 26 and 30 of instant application is interpreted as "An isolated host cell *in vitro*" based on the election of Group I, not Group II (which reads on a host cell *in vivo*).

With regard to cytoplasmic signaling molecule that comprises least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from human inducible co-stimulator (claims 1 and its dependent claims 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, and 30 of instant application), Maher et al. teach a recombinant chimeric TCRζ/CD28 receptor bearing hybrid TCRζ/CD28 cytoplasmic signaling domain, expressed from retroviral vectors (See Title, Fig. 1 [CD3ζ diagramed in P28Z construct is a TCR, T cell receptor], and Recombinant receptors and retroviral vector, Experimental protocol, page 74, Maher et al, 2002).

With regard to chimeric receptor protein comprising an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic signaling domain (claims 18, 19 of instant application), and the extracellular ligand-binding domain being an antibody, or an antigen-binding fragment (claim 21 of instant application), Maher et al. teach chimeric TCRζ/CD28 receptor comprising scFv coupled through human CD8α hinge and transmembrane sequences to the intracellular domain of human TCRζ (See Fig. 1, page 71, and Experimental protocol, page 74, Maher et al, 2002).

With regard to a vector (claim 25 of instant application) or a host cell comprising the recited nucleic acid molecule in claim 1 (claims 26, 28, and 30 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells --- Peripheral blood mononuclear cells from healthy donors (See Experimental protocol, page 75, Maher et al, 2002).

With regard to acceptable excipient (claim 37 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells (See Experimental protocol, page 75, Maher et al, 2002), and thereby any inactive substance, other than the nucleic acid sequences encompassed by the retroviral vector, is considered as acceptable excipient, which includes water.

Maher et al. does not teach "the cytoplasmic signaling sequences comprising the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLDVTL (SEQ ID NO 1)".

Hutloff et al. teach that ICOS and CD28 (the cytoplasmic signaling sequence of which is used by Maher) are functionally related, homologous proteins that enhance T cell responses/activation to foreign antigen. Hutloff et al. teach the claimed SEQ ID No: 1 is the cytoplasmic signaling sequences of ICOS (inducible co-stimulator) and provides the amino acid sequence alignment between human ICOS and CD28, which demonstrated conserved amino acid throughout ICOS and CD28 sequences including C-terminal cytoplasmic signaling domain 166-199 of ICOS, i.e. SEQ ID No: 1 (See Fig. 1d, Hutloff et al., 1999). Hutloff et al. further teach that ICOS matches the ability of CD28 to amply the secretion of many lymphokines and is superior to CD28 in induction of IL-10 important for co-stimulatory activity during T- cell activation (See bridging paragraph, pages 265-266, Hutloff et al., 1999).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Maher et al. regarding chimeric TCRζ/CD28 receptor bearing hybrid TCRζ/CD28 cytoplasmic signaling domains expressed from retroviral vectors with the teachings by Hutloff et al. regarding functional relatedness between the cytoplasmic signaling sequences of ICOS and CD28, as well as the superior characteristics of ICOS, to arrive at the nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences comprises the sequence KKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL (SEQ ID NO: 1), the cytoplasmic signaling sequence of ICOS, as claimed.

One having ordinary skill in the art would have been motivated to combine the teachings of Maher et al. with the teachings of Hutloff et al. because Hutloff et al. teaches that ICOS and CD28 are functionally related homologous proteins that enhance T cell responses/activation to foreign antigen, and ICOS matches the ability of CD28 to amply the secretion of many lyphokines and is superior to CD28 in induction of IL-10 important for co-stimulatory activity during T- cell activation.

There would have been a reasonable expectation of success given (i) successful demonstration of human T-lymphocyte cytotoxicity and proliferation directed by a chimeric TCRζ /CD28 receptor by the teachings of Maher et al., and (ii) the identification and characterization of ICOS being a functionally related homologous protein of CD28 and being is superior to CD28 in the induction of IL-10 important for co-stimulatory activity during T- cell activation by the teachings of Hutloff et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

10. Claim 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maher et al. (Maher et al., Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor. *Nat Biotechnol.* 20(1): 70-5, Jan. 2002; listed in the IDS filed by the applicants) in view of Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants) as applied to claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 above, and further in view of **Finney et al.** (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002, listed in IDS filed by the applicants).

The teachings of Maher et al. and Hutloff et al. have been discussed in the preceding section of the rejection of claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 under 35 U.S.C. 103(a) as being unpatentable over Maher et al. in view of Hutloff et al.

None of Maher et al. and Hutloff et al. teaches "a cytoplasmic signaling molecule that comprises three cytoplasmic signaling sequences" as recited in claim 8 of instant application.

Finney et al. teaches a nucleic acid encoding a cytoplasmic signaling molecule comprising three cytoplasmic signaling sequences derived from TCRζ, CD28, and CD137 (See page 7, claim 8, Finney et al., 2002). Finney et al. further teaches the presence of multiple cytoplasmic signaling sequences in a cytoplasmic signaling molecule can increase the efficiency of mediating signal transduction through the receptors from which the cytoplasmic signaling sequences are derived (See page 8, Finney et al., 2002).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Finney et al. regarding increasing the efficiency of mediation of signal transduction by the presence of multiple cytoplasmic signaling sequences derived from TCRζ, CD28, and CD137 in a cytoplasmic signaling molecule, into the combined teachings of Maher et al. and Hutloff et al. directing to a chimeric TCRζ/ICOS or TCRζ/CD28 receptor in mediation of T-cell activation to arrive at the claimed nucleic acid encoding a cytoplasmic signaling molecule comprising three cytoplasmic signaling sequences.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Finney et al. into the combined teachings of Maher et al. and Hutloff et al. because Finney et al. teaches increasing the efficiency of mediation of signal transduction by the presence of multiple cytoplasmic signaling sequences derived from TCRζ, CD28, and CD137.

There would have been a reasonable expectation of success given (i) successful demonstration of Human T-lymphocyte cytotoxicity and proliferation directed by a chimeric TCRζ /CD28 or TCRζ /ICOS receptor by the combined teachings of Maher et al. and Hutloff et al., and (ii) the demonstration of increased the efficiency of mediation of signal transduction by the presence of three cytoplasmic signaling sequences derived from TCRζ, CD28, and CD137 in a chimeric cytoplasmic signaling molecule by the teachings of Finney et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments

Applicant argues that Roberts et al. did not disclose nucleic acid molecules that encode a chimeric receptor protein which includes an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling sequence comprising the particular sequence of amino acid residues 166 to 199 of the human inducible co-stimulator. An applicant argues that, with the presently incorporated SEQ ID, the rejection is overcome. Applicant presents the same arguments for rejection anticipated by Finney et al as well as by Maher et al.

In response, the Examiner agrees with Applicant on that the incorporated SEQ ID No: 1 is not taught by Roberts et al., Finney et al. or Maher et al. Therefore, the 102 rejections have been withdrawn. However, Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999) teaches SEQ ID No: 1 as indicated in the new 103 rejections presented above.

Conclusion

11. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30

PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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